Supporting Statement A for:

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (NCI)

Revision Request for OMB #: 0925-0407

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Yellow highlights indicate changes since the approval of the 2012 submission.

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This is a request for a revision of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) for three years. This trial was designed to determine if cancer screening for prostate, lung, colorectal, and ovarian cancer can reduce mortality from these cancers which caused an estimated 253,320 deaths in the U.S in 2014. The design is a two-armed randomized trial of men and women aged 55 to 74 at entry. OMB first approved this study in 1993 and has approved it every 3 years since then. Recruitment was completed in 2001, baseline cancer screening was completed in 2006, and data collection continues on the current cohort of 77,281 participants who are actively being followed. The additional follow-up will provide data that will clarify further the long term effects of the screening on cancer incidence and mortality for the four targeted cancers. Further, demographic and risk factor information may be used to analyze the differential effectiveness of cancer screening in high versus low risk individuals.

A. JUSTIFICATION

A.1. Circumstances Making the Collection of Information Necessary

The Early Detection Research Group of the Division of Cancer Prevention, National Cancer Institute (NCI), developed the concept of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (OMB Number: 0925-0407; Expiration Date: December 31, 2015) in accordance with their mission to develop scientific information and concepts and disseminate the acquired knowledge regarding early detection techniques, practices, and strategies to reduce mortality and morbidity from cancer. To this end, the Research Group sponsors and conducts clinical trials and other appropriate research, fosters technology development, and encourages publication of scientific findings and adoption of proven early detection practices. Section 412 of the Public Health Service Act (42 USC *§* 285a-1) authorizes the collection of the information.

According to the American Cancer Society "Cancer Facts and Figures 2014" (http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/), in 2014 there were an estimated 50,310 deaths from colon cancer and 159,260 deaths from lung cancer. About 14,270 women died from ovarian cancer and 29,480 men from prostate cancer. Lung and colon cancers account for over one-third of all cancer deaths in the United States. Successful screening programs for these cancers could possibly have a major impact on overall cancer mortality in the U.S.

OMB first approved the PLCO Cancer Screening Trial in October 1993. Since that initial approval, OMB approved the trial in 1996, 1999, 2002, 2005, 2008, 2011, and 2012. During the first

approval period a two-year pilot study was conducted to evaluate recruitment methods and data collection procedures. Participants who were recruited during the pilot were included in the main study. PLCO trial recruitment ended in 2001, cancer screening was completed in 2006, and to date, approximately half of participants have completed 14 or more years of follow-up. In March 2009, the first report on cancer screening and prostate cancer mortality was published in the *New England Journal of Medicine* (Andriole et al., 2009). In October of the same year, investigators from the Cancer Genetic Markers of Susceptibility (CGEMS) initiative reported in *Nature and Genetics* the results of a third genome-wide association study leading to the identification of a new prostate cancer susceptibility locus on chromosome 8q24 (Yeager et al., 2009). PLCO biospecimens and data were used in this CGEMS study. Also both the report on screening and ovarian cancer mortality and the report on screening and lung cancer mortality were published in the *Journal of the American Medical Association* (Buys et al., 2011; Oken et al., 2011). In addition, the effect of screening on prostate cancer mortality after 13 years of follow-up was published in the *Journal of the National Cancer Institute* (Andriole, 2012). The report on screening and colorectal cancer mortality was published in the *New England Journal of Medicine* (Schoen et al., 2012). Since the inception of the trial, there have been more than 351 articles published in peer-reviewed journals; and the number of investigators that submit applications requesting use of PLCO biospecimens and data increases every year. In addition to publications of benefit to the scientific community, data collected will be used to evaluate the effect of screening on the reduction of cancer specific mortality from the four targeted sites: prostate, lung, colorectal, and ovary.

The NCI seeks to increase the value of PLCO as a resource to intra- and extra-mural researchers by continuing to collect follow-up behavioral data, morbidity and mortality outcomes, and tumor tissue. Given the advanced age of participants with at least 14 years of follow-up, the PLCO is entering its most productive years of cancer and vital status ascertainment. These additional data will clarify further the long-term effects of cancer screening on cancer mortality, and enable new studies of rare tumors and common tumors in subpopulations.

This request is for the ongoing data collection for years twenty-four through twenty-six of the study. The contracts for all 10 Screening Centers (SCs) ended by 2014. NCI has awarded a contract for continuation of participant follow-up activities to one data collection site named the PLCO Central Data Collection Center (CDCC). The CDCC will conduct all active data collection to ascertain cancer and vital status with participants, relatives, physicians, and medical records and pathology departments for those participants who agreed to be followed by the CDCC. The CDCC will also conduct passive data collection, i.e., submission to tumor registries, and the National Death Index (NDI), for participants who transferred to the CDCC and participants who are lost to follow-up or deceased, and it will coordinate passive data collection by the former SCs for participants who agreed to continued follow-up, but did not agree to be contacted by a new data collection site.

With the extensive questionnaire and clinical data and the rich collection of biospecimens collected at multiple time points before and after cancer diagnosis, the PLCO Trial has proven to be an extremely valuable resource for research in cancer prevention and molecular epidemiology. Etiologic and early marker studies are being carried out to address hypotheses concerning potential carcinogenic and anti-carcinogenic exposures and genetic susceptibility to disease risk. Biochemical and genetic studies of cancer etiology will typically involve comparison of risk factors between cases and a similar number of comparison subjects. Studies to evaluate the natural history of disease and to characterize early markers will be carried out utilizing previously sequentially collected samples to relate biochemical changes in blood to the pre-diagnostic course of disease development. The etiology and early marker component is fully integrated with the early detection component of the Trial and was explained to participants. They were offered the opportunity to participate in these additional studies of cancer and other diseases which affect their age group. Participation in the additional studies was completely voluntary.

A.2. Purpose and Use of the Information

Trials adequate to answer questions of risk and benefit of the cancer screening modalities used in this trial have not been previously conducted in the United States, so there is no other source from which to

obtain the data. The scientific goals, design, and clinical process for generating the data have been subjected to multiple peer reviews. Contamination in the control arm and noncompliance in the screened arm were explicitly considered in the statistical design. Anticipated levels of contamination and non-compliance were estimated from available literature and are monitored during the trial. The sizes of the mortality differences between screened and control arms for each cancer site detectable in the trial were determined in the presence of anticipated levels of contamination and non-compliance. The PLCO Screening Trial was designed to achieve maximum financial efficiency while achieving the scientific goals of the research. Separate trials to answer the questions of screening effectiveness in the four cancer sites (prostate, lung, colorectal, and ovary) individually would have cost two to four times as much due to replication of study infrastructure. The technologies being tested were of current interest, because they were being considered by clinicians for screening. The PLCO primary endpoint is cancer-specific mortality for each of the four cancer sites. In addition, cancer incidence, stage shift, and case survival are to be monitored to help understand and explain the results. Biologic prognostic characteristics of the cancers were measured and will continue to be correlated with mortality to determine the mortality predictive value of these intermediate endpoints.

Basic demographic, screening history, and risk factor data for the four cancer sites, as collected from all participants at baseline, will be used to assure comparability between the screening and control groups and make appropriate adjustments in analysis. Further, demographic and risk factor information will be used to analyze the differential effectiveness of cancer screening in high vs. low risk individuals. It is also important to have this baseline data in order to characterize participants who drop out of the study.

It is critical that the PLCO participants continue to be followed to determine the long term effects of screening on incidence and mortality for the four target cancers. During the past three years, ongoing data collection has consisted of ascertaining and confirming new cancers and determining vital status for each participant. The data collection instruments included the Annual Study Update (**Attachment 1**), the Health Status Questionnaire (**Attachments 2A and 2B)** and the Medication Use Questionnaire (MUQ) (**Attachment 4)** all of which are self-administered.

The Health Status Questionnaire is gender specific and is mailed annually to a subset of 2,000 participants. The Annual Study Update is mailed to all active participants. The MUQ was administered once during the last approval period.

A.3. Use of Improved Information Technology and Burden Reduction

Computer-assisted telephone interviewing for the data collection instruments, including the Annual Study Update (ASU), Health Status Questionnaire (HSQ), and the Medication Use Questionnaire (MUQ) was not considered appropriate given their proposed method of administration. These instruments are self-administered and are mailed to the participant to complete at home. This mode of administration is necessary given the large number of participants. Telephone administration is usually limited to non-responders. In cases where telephone administration is used, the staff person introduces him/herself, explains the reason for the call, and asks if it is a good time for the participant to answer a couple of questions (**Attachment 5**). The ASU is read to the participant verbatim; exactly as the data collection items are written.

In addition, for the Annual Study Update, self-administration is advantageous in order to minimize contact with the control group and thus reduce potential for contamination (e.g., controls deciding to have screening examinations because of their involvement with a screening trial).

A previous Privacy Impact Assessment (PIA) was completed and published by HHS on February 22, 2011 for the IT system being used to store and monitor data. The system name is "NIH NCI PLCO Research Database (PLCO)" (**Attachment 6**). The computerized data management system reduces respondent burden. Information collected at baseline is stored in the system. For subsequent annual information collections, information previously supplied by the participant is pre-populated and sent to him/her for confirmation (e.g. name and address of primary care physician and tracing contacts). The participant only needs to indicate whether the information is still correct and not repeat unchanged information. The Annual Study Update shows a computer generated reference date after which the

participant is asked to provide cancer diagnosis information; diagnosis information for prior periods need not be repeated.

A.4. Efforts to Identify Duplication and Use of Similar Information

This trial was four years in design. Consultations with expert groups regarding each of the four cancer sites were numerous. Presentations to professional groups, NCI-sponsored workshops, external and internal peer review of the concept, a comprehensive review of the literature (**Attachment 7**) and interactions with investigators in European countries interested in these research questions, were aggressively pursued in the design and concept development effort. NCI staff involved in the design of this trial also participated in the screening evaluation project of the International Union Against Cancer which monitored and assessed the status of cancer screening worldwide. This is the first, and possibly only, study in the world to evaluate these multiple screening modalities in a randomized, controlled trial. No similar data are available to answer the questions addressed in the PLCO trial. There is no duplication, although since the PLCO trial has entered its main phase, some European countries are collaborating in the evaluation of prostate cancer screening by a protocol unique to their needs, and once-in-a-lifetime screening by flexible sigmoidoscopy, and screening for ovarian cancer using a different protocol are being evaluated in the United Kingdom. In addition, the evaluations of cancer screening programs in Korea and Japan have been published.[1, 2]

A.5. Impact on Small Businesses or Other Small Entities

This information collection does not involve small businesses or other small entities.

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[1] Jung KW, Shin HR, Kong HJ, Park S, Won YJ, Choi W, Park EC (2010). Long-term Trends in Cancer Mortality in Korea (1983-2007): A Joinpoint Regression Analysis. Asian Pacific Journal of Cancer Prevention, 11, 1451-1457

[2] Yoshida M, Kondo K, Tada T (2010). The relation between the cancer screening rate and the cancer mortality rate in Japan. The relation between the cancer screening rate and the cancer mortality rate in Japan. The Journal of Medical Investigation, 57, 251-259.

A.6. Consequences of Collecting the Information Less Frequently

Annual follow-up provides timely information on incidence of new cancers and deaths from the cancers of interest. Less frequent follow-up would be deleterious to monitoring requirements. Current participant files are essential to minimize loss to follow-up and ensure timely acquisition of endpoint events.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The proposal is consistent with the information collection guidelines in 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A 60-day Federal Register notice soliciting comments on the PLCO trial prior to submission to OMB was published in the Federal Register on April 21, 2015, Vol. 80, P. 22211. No comments were received.

The PLCO Steering Committee was involved in designing, conducting, and monitoring the PLCO trial. The committee provided overall scientific direction for the study and served as the major decision-making body for operations. The Steering Committee was disbanded when the majority of the screening center contracts ended in September 2011.

Data were reviewed on a regular basis by the Data Safety Monitoring Board (DSMB) for PLCO. Given the final results for all four cancers were either published or being prepared for publication, the DSMB dissolved following their meeting on December 2, 2011.

A.9. Explanation of Any Payment or Gift to Respondents

This information collection does not involve payment or gifts to respondents.

A.10. Assurance of Confidentiality Provided to Respondents

Each participant recruited into the study signs an informed consent that states the voluntary nature of participation and states that the information they provide will be kept private to the extent of the law. The Privacy Act does apply to this information collection. The identity of participants is maintained in a number of different ways.

- Access to study data is limited to the staff working on the study.
- All completed hard-copy data forms are kept in locked filing facilities at CDCC and SC offices or special archive facilities.
- Data collected at the CDCC and SCs are maintained in automated information systems physically separate from other institutional systems. Limited (no personal identifiers available) dial-in access is possible through a two-step procedure requiring the CDCC and SC. The systems have the following privacy controls: Access to files is through the use of a password known only to authorized study staff. Names and Social Security Numbers (SSN) are encrypted and stored in separate files from other data and are linked only by the participant identification number. All reports or files (output) with identifiers, produced and maintained at the SCs only, carry the following disclosure statement at the top and bottom of each page: *"This report contains data protected under the Privacy Act of 1975. Please distribute only to authorized personnel and store and dispose of report in a proper manner."*
- Data collected are maintained at the CDCC and SCs (including identifying information) and at NCI (without identifying information) until completion of the study or until they are no longer required for the research. Data will be destroyed as required by NIH Manual 1743 - "Keeping and Destroying Records".

Each SC had Institutional Review Board (IRB) approval, as well as Office of Human Research Protocol (OHRP) certification before beginning participant recruitment. Data transfer from the SC to the CDCC did not occur until both organizations had IRB approval. At the time of study initiation, NCI and the Coordinating Center (CC) IRBs determined that IRB review was not needed since neither receives any identifying information about the participants. However, both the Westat and NCI IRBs have approved

the CDCC activities. These approvals are kept current by standard procedure and are documented in **Attachment 9**. The SC IRB approvals are kept current by standard procedures and are documented in **Attachment 9**. The data collection is covered by NIH Privacy Act Systems of Record 09-25-0200, "Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD" published in the Federal Register on September 26, 2002 (67 FR 60776) (**Attachment 10**).

A.11. Justification for Sensitive Questions

Personally identifying information (PII) on PLCO trial participants is collected and maintained by the CDCC and the SCs, and is necessary to allow annual follow-up, to access medical records, and to perform National Death Index and cancer registry searches. No identifying information is provided to the government. Data analyses and reports are aggregated without personal identifiers.

The only potentially sensitive question is SSN. SSN is only collected on the Follow-up Locator Form which is the second half of the ASU (**Attachment 1**), and confirmed annually by the participant. SSN is used, as stated on the form, only to help locate participants if no longer at their home address and to search the National Death Index and cancer registries in the future, which is essential to the validity of the study results. When SSN is requested, the participant is told of the purpose of the data collection, the legislative authority under which the information is being collected, the voluntary and private nature of the survey, and the absence of any penalty for refusal. SSN is not required for participation in the study.

SSN data are maintained at the CDCC and each SC and are stored with other confidential study data and are subject to the same confidentiality procedures and protections as required by the Privacy Act Systems of Record (**Attachment 10**) and as summarized in the study-specific Confidentiality Procedures of Screening Centers (example provided in **Attachment 11**).

A.12. Estimates of Annualized Burden Hours and Costs

It is estimated that the annualized burden to complete the ASU, HSQ, and MUQ, the follow-up telephone script for ASU non-responders, and the Authorization to Obtain Medical Records will be 26,320 hours for 77,281 respondents. This amounts to an estimated total of 78,960 burden hours for the respondents over the 3 years of data collection (Table A.12-1). In the 2012 OMB PLCO Cancer Screening Trial submission, the estimated number of annual respondents was 94,000. The decrease in the number of respondents is due to deaths among the cohort and to an overestimate of the number of participants who consented to active follow-up from the ten screening centers.

Table A.12-1 Estimates of Annual Burden Hours

Type of Respondents	Number of Respondents	Number of Responses per Respondent	Average Time Per Response (Minutes/Hour)	Annual Burden Hours
Participants who complete the ASU **(Attachment 1)**	77,281	1	5/60	6,440
Non Responders to the ASU **(Attachment 5)**	3,091	1	5/60	258
Participants who complete Authorization to Release Medical Records (**Attachment 11**)	2,700	1	3/60	135
Male Participants who complete the HSQ **(Attachment 2a)**	1,040	1	5/60	87
Female Participants who complete the HSQ **(Attachment 2b)**	960	1	5/60	80
Participants who complete the MUQ **(Attachment 4)**	77,281	1	15/60	19,320
Total				26,320

The annualized respondent burden is estimated at 26,320 hours at $22.33/hour, amounting to an annualized cost to respondents estimated to be $587,716 (Table A.12-2). The hourly wage rate, $22.33, is based on the Bureau of Labor Statistics http://www.bls.gov/oes/current/oes_nat.htm#00-0000 for "All Occupations", occupation code: 00-0000. For the 3 years of data collection, the total estimated cost to respondents will be $1,763,148.

Table A. 12-2 Annualized Cost to Respondents

Type of Respondent	Total Number of Respondents	Frequency of Responses	Average Time per Response	Hourly Wage Rate	Total Respondent Cost
Participants who complete the ASU (**Attachment 1**)	**77,281**	**1**	**5/60**	**$22.33**	**$143,807.06**
Non Responders to the ASU **(Attachment 5)**	**3,091**	**1**	**5/60**	**$22.33**	**$5,751.84**
Participants who complete Authorization to Release Medical Records (**Attachment 11**)	**2,700**	**1**	**3/60**	**$22.33**	**$3,014.55**
Male Participants who complete the HSQ (**Attachment 2a)**	**1,040**	**1**	**5/60**	**$22.33**	**$1,935.27**
Female Participants who complete the HSQ (**Attachment 2b**)	**960**	**1**	**5/60**	**$22.33**	**$1,786.40**
Participants who complete the MUQ (**Attachment 4**)	**77,281**	**1**	**15/60**	**$22.33**	**$431,421.18**

Total	**$587,716.30**

A.13. Estimate of Other Total Annual Cost Burden to Respondents and Record keepers

There is no other total annual cost burden to respondents or record keepers for capital or start-up costs, or for operation, maintenance, or purchase of services.

A.14. Annualized Cost to the Federal Government

The total average annualized cost to the Federal Government is $2,244,997 (Table A.14.1). Annual costs include costs for contractors: the CDCC; and NCI staff time. NCI staff, estimated at four full–time equivalents, will consist of one step 5, grade level 13; two step 5, grade level 14s; and one step 5, grade level 15, all of whom are program directors. The NCI staff members will be responsible for carrying out planning and design activities, monitoring the project and conducting analyses at a cost of approximately $489,218 per staff year. This is an estimated reduction in total cost ($5,402,138) in the last submission as a result of the discontinuation of funding the screening centers and consultants. These figures include direct and indirect costs.

Table A.14-1 Annual Cost to the Federal Government

	YEAR 24 (2016)	YEAR 25 (2017)	YEAR 26 (2018)
Central Data Collection Center	$1,716,430	1,750,759	$1,785,774
TOTAL CONTRACTOR	$1,716,430	$1,750,759	$1,785,774
NCI Staff			
Program Director, Step 5, GS 13 100% FTE	$102,932	$103,961	$105,000
Program Director, Step 5, GS 14 100% FTE	$121,635	$122,851	$123,810
Program Director, Step 5, GS 14 100% FTE	$121,635	$122,851	$123,810
Program Director, Step 5, GS 15 100% FTE	$143,079	$144510	$145,955
ANNUAL COST	$2,	$2,24	$2,28

	205,711	4,932	4,349

A.15. Explanation for Program Changes or Adjustments

This is a revision. The number of responses to the follow up forms in the PLCO is consistently declining because more deaths are occurring as the study participant's age. In 2011, the estimated number of annual responses was 191,600; a substantial increase from the previous submission because a new questionnaire, the Supplemental Questionnaire (SQX), was introduced (30 minutes to 93,000 respondents). In 2012 the number of annual responses was 193,760 a slight increase from the previous submission due to an overestimate of the number of participants who consented to active follow-up from the first eight screening centers. The current number of annual responses estimated for this submission is 162,353.

This is a continued follow up of an existing cohort as a result there will not be any new participants recruited into the study and thus no longer a need for a consent form. The Authorization to Release Medical Records (**Attachment 11**) will continue to be completed by anyone who reports a new cancer diagnosis on an ASU as in previously approved iterations of this information collection. It allows the CDCC to obtain a copy of the participants' medical record for abstraction.

The total number of burden hours has decreased since the last submission primarily due to the number of deaths among the cohort and overestimate of the number of participants who consented to active follow-up from the ten screening centers.

A.16. Plans for Tabulation and Publication and Project Time Schedule

Methods to be employed in the analysis of the study will include standard descriptive statistics and analytic techniques such as regression, analysis of variance and covariance, analysis of proportions, and contingency tables. New methods of analysis or modeling will be developed and applied as needed. Data are optically scanned and, when appropriate, manually entered daily. Quality assurance is monitored locally.

Sensitivity, specificity, and predictive value will be calculated for each test and test combination for each cancer site for each screen. Prevalence will be calculated as the number of cancers detected per 1000 individuals screened on the first screen for each cancer site and SC and pooled to indicate overall prevalence. Incidence will similarly be calculated as the number of cancers per 1000 person years at risk. Incidence rates will be calculated yearly and cumulatively over the course of the trial. The ratio of prevalence to incidence will be used as an estimate of the mean duration of pre-clinical disease.

For cancer case characteristics such as histology and stage which carry prognostic implications, the distribution of each characteristic will be calculated for each cancer site among control group cases, all screened group cases, screen detected cases, and interval cases. The distributions can be compared using Chi-square (χ^2) tests. Survival distributions will also be calculated for the same subsets of cancer cases using the Kaplan-Meier method and compared using the log rank test and Cox proportional hazards regression methods. These distributions will be calculated cumulatively each year of the trial to assess possible screening benefit. These intermediate endpoints cannot be relied upon for definitive evaluation, however, because they are subject to lead time and length biases.

Lead time is the amount of time by which a cancer is diagnosed earlier in a cancer screening program relative to the time when it would present clinically in the absence of screening. If survival is measured from time of diagnosis, cases of disease detected by screening will automatically have longer survival, even if length of life is not increased, because of the inclusion of the lead-time. This is lead-time bias. Length bias is related to the fact that in a population of individuals with a disease, there is a distribution of times or durations which the diseased individuals spend in a pre-clinical disease state in which the disease is asymptomatic but detectable by screening. Individuals with longer duration and therefore slower growing, better prognosis disease are more likely to be in the pre-clinical detectable state at the time of a screen. As a result, cases of disease which have a better prognosis even in the absence of screening are over-represented among the screen-detected case group. Any measure of staging or survival is improved as a consequence of this length bias even if screening has no effect on disease outcome.

Estimation of lead-time is an important intermediate indicator of early detection capability of the screening procedures. Average lead-time will initially be estimated using the prevalence to incidence ratio under the assumption of an exponential distribution of pre-clinical duration. Other modeling approaches to lead time estimation also will be employed. These include the Day-Walter model (Am J Epidemiol 118:865-886, 1983 and Biometrics 40:1-14, 1984) which allows estimation of the lead time distribution, and newer approaches under development which examine differences in long term case survival rates to estimate mean lead time. The assumption of an exponential distribution is justified by several analyses of screening data, using the Day-Walter model and other approaches, in which the exponential was the best fitting distribution. Other, more general, lifetime distributions will also be considered including the Weibull, gamma, and generalized gamma distributions.

As with incidence rates, the rate of advanced stage disease and the cause-specific and all cause mortality rates will be calculated as the number of events per 1,000 person years at risk. These will be calculated yearly and cumulatively for each successive year of the trial, and relative to each of the four cancer sites under study. The rate of advanced stage disease is thought to be an indicator of changes in disease specific mortality, while the cause specific death rate is the primary endpoint in this trial. These rates will be compared using Poisson tests and Poisson regression analysis. All cause mortality is examined as an indicator of comparability of the randomized arms of the trial.

Complications of the screening and diagnostic procedures administered to trial participants were recorded and monitored very closely during the active screening phase of the trial. These include any medical complications or risks and any mortality potentially related to study procedures, particularly the more invasive procedures such as colonoscopy or laparotomy, which might follow a positive colorectal screen or ovarian screen, respectively. These were examined for each cancer site at each SC for up to one year after a screening episode. Cancer incidence is also tracked to alert investigators to possible substantial over-diagnosis of one of the cancers being studied. This is thought to be a problem particularly for prostate cancer. Guidelines for termination in the event of adverse effects of the screening process were developed by the DSMB.

The PLCO trial was designed to obtain a racially mixed study population which will permit valid scientific evaluation of each of the screening modalities under study for all races combined. In designing this trial, it was not considered feasible to conduct mortality endpoint trials by minority subgroup. Such an objective would have necessitated running an equivalent trial for each of the subgroups. Race was recorded at baseline for all PLCO trial participants. Post hoc subgroup analyses to ascertain the degree to which effectiveness is equivalent or different in racial subgroups can therefore be conducted. If all race specific findings are consistent with the overall finding, generalization of the overall results to all racial groups would be valid. If not, additional research hypotheses can be considered.

Publications addressing all of the above topics will be submitted to appropriate medical, statistical, and clinical trials journals as the relevant data reach maturation. A steady stream of publications is anticipated as the trial progresses to ensure that the medical and scientific communities are kept fully informed. To date, 351 articles and book chapters have been published from PLCO data (**Attachment 12**).

The time schedule for the ongoing project is provided below.

Activities	After OMB Approval (Months)
Continued Cancer Ascertainment	0-36 months
Continued Vital Status Ascertainment	0-36 months
Continued Data Editing	0-36 months
Continued Data Analysis	0-36 months
Continued Publication of Findings	0-36 months

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

This study will display the expiration date for OMB approval of the information collection.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

PLCO complies with 5 CFR 1320.9, the Certification for Paperwork Reduction Act Submissions.